

REMARKS

Claims 1, 3-6, 8-15, 20, 24-27, 30 and 31 are pending in the instant application. The Examiner has cited various informalities in claims 1, 8-10, 12, 15, 20 and 31. Claims 4, 5, 27 and 30 stand rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3-6, 8, 9, 11-15, 20, 27 and 30 stand rejected under 35 USC § 112 as being unpatentable over Yu [US 6103492] in view of Buck *et al* ["Photochemically induced dynamic nuclear polarization[...]" *Biochemistry* 77(9) pp5145-8]. The application has been amended. The claims have been amended. Applicant respectfully submits that none of the amendments introduce new matter in contravention of 35 U.S.C. § 132. Reconsideration is respectfully requested.

Claim Rejections – informalities

The various informalities outlined in respect of claims 1, 8-10, 12, 15, 20 and 31 have been taken into account and the certain suggested amendments have been made.

Applicant respectfully submits that the Examiner's objections to certain terms, namely 'hyperpolarising', 'hyperpolarisation', 'analysing', 'analysed', 'hybridisation', 'polarisation', etc., are improper as each of these terms is well understood in the English language and as used in the instant application. As support, Applicant submits photocopied pages 41 and 900 of Merriam-Webster's Collegiate Dictionary, Tenth Edition, for definitions of the words 'analyse' and 'polarize' showing that each are simply British variants of 'analyze' and 'polarize'. Additionally, Applicant directs the Examiner's attention to United States Patent Nos. 7,186,550 and 7,107,169 as merely two examples of the word 'hybridisation' being used in the very first issued claim. Applicant notes that many more patents have issued using these very same terms in their claims, indicating their acceptability.

In view of the amendments and remarks hereinabove, it is respectfully submitted that each of the noted objections have either been obviated by amendment or traversed as being improper. Reconsideration and withdrawal of the objections is respectfully requested.

Claim Rejections – 35 USC § 112

Claims 4, 5, 27 and 30 are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 have been amended such that the term “artificially high concentration” has been replaced with the term “artificially-enriched abundance”. The replacement term finds basis in the application as filed on page 3 lines 25-28 as well as on page 6 lines 15-32. Applicant submits that the teaching of the specification provides ample guidance to the skilled person as to what the term “artificially-enriched abundance” means.

Claim 27 has been amended such that the wording reflects that in the specification as filed on page 17 lines 30-32. Applicant submits that “no well, surface or container” does not require antecedent basis as re-worded and also that the phrase now clearly applies only to the aerosol.

Claim 30 in its present form is not regarded by Applicant as being indefinite for the reasons outlined by the Examiner. Applicant respectfully submits that the Examiner’s argumentation is flawed in that claim 30 does not encompass both a broad range and a narrow range. Claim 30 definitively encompasses one preferred value from the range set out in claim 5, i.e. “one specific position” as a preferred value from “up to 10 defined positions”. It is Applicants belief that the limitation of claim 30 is thus abundantly clear to one of ordinary skill in the art.

In view of the amendments and remarks hereinabove, Applicant respectfully submits that each rejection under 35 USC § 112, second paragraph has been traversed. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections – 35 USC § 103

Claims 1, 3-6, 8, 9, 11-15, 20, 27 and 30 are rejected under 35 USC § 112 as being unpatentable over Yu [US 6103492] in view of Buck *et al* [“Photochemically induced dynamic nuclear polarization[...]” *Biochemistry* 77(9) pp5145-8]. The rejection is respectfully traversed.

As stated by the Examiner, neither Yu nor Buck teach that the degree of hyperpolarisation of the NMR active nucleus is in excess of 0.1%. However, the Examiner contends that to get from the combined teachings of Yu and Buck to the subject matter of claim 1, the skilled person would only need to use routine skill in the art. In response to Applicant’s previous arguments filed September 18 2006, the Examiner is not persuaded that claim 1 is inventive over the teachings of the prior art. The Examiner contends that the assay performed by Buck is only an example of a hyperpolarisation assay rather than being a limitation on the technique disclosed by Buck. The Examiner further contends that there is no showing by the Applicant that the hyperpolarisation technique is any different from that disclosed by Buck.

Applicant respectfully contends this assertion. The method of Buck is photochemically-induced dynamic nuclear polarization [CIDNP] in which the NMR signal intensity is enhanced by contact of a sample with a photoexcited dye. As presented in Applicant’s response dated September 18 2006, the level of polarization achievable with this method is in the order of 0.6% above equilibrium. Furthermore, for the assay of Buck, this method of enhancing polarization is particularly suitable as it specifically enhances the NMR signal intensities of the aromatic amino acids that the assay of Buck wishes to analyze [see page 5145 column 2 second paragraph of Buck]. In the present invention, hyperpolarisation may be carried out using a variety of techniques, such as polarisation transfer from a noble gas, “brute force”, DNP and the para-hydrogen method. As outlined in detail on page 1 line 31 to page 2 line 29, all of these methods are qualitatively different from CIDNP in that they do not involve contact of the sample with a photoexcited dye. These hyperpolarisation methods are all capable of achieving polarisation levels of at least 0.1% above equilibrium.

Applicant therefore respectfully contends that the polarisation technique presented by Buck is different to those presented in the present invention. In addition, given that the polarisation technique of Buck is particularly suited to the assay described therein, the skilled person would not be motivated to use a different polarisation method. For these reasons, Applicant respectfully submits that claim 1 of the present invention is patentably distinct over Yu in view of Buck and respectfully requests that the rejection should be withdrawn.

All the arguments presented by the examiner in rejection of claims 3-6, 8, 9, 11-15, 20, 27 and 30 are based on the premise that claim 1 is unpatentable over Yu in view of Buck. Applicant respectfully submits that as claim 1 is patentable over Yu in view of Buck for the reasons presented above, each of claims 3-6, 8, 9, 11-15, 20, 27 and 30 are also patentable over the cited prior art. Reconsideration and withdrawal of these rejections are respectfully requested.

In view of the amendments and remarks hereinabove, Applicant respectfully submits that the instant application, including claims 1, 3-6, 8, 9, 11-15, 20, 27, and 30, is allowable over the prior art. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

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UPDATED ANNUALLY

**Merriam-
Webster's
Collegiate
Dictionary**

TENTH EDITION

- **Clear and precise**
- **Best guidance on word choice**
- **Most definitions—over 215,000**



(10) **Patent No.:** US 7,107,169 B2
(45) **Date of Patent:** Sep. 12, 2006

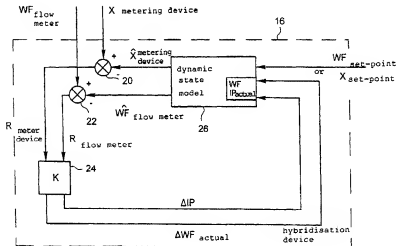
- a mass flow meter,
a hybridisation device for determining an actual mass flow of fluid comprising:
a first input comprising a set-point value (WF set-point, Xset-point),
a prediction unit (26) capable of determining, from the first input and variables of state comprising the actual mass flow (WF actual) and parametric unknowns (IP), estimated values ('WF flow meter, Xmetering device),
a second input comprising the measured position of the metering device (Xmetering device) and the measured mass flow of fluid (WF flow meter),
a calculation residues (30, 22, 20) for determining a first residue (Rmetering device) between the measured position of the metering device and the estimated position of the metering device and a second residue (Rflow meter) between the measured mass flow of fluid and the estimated mass flow of fluid,
a correction unit (24) for determining, from the first and second residues corrections capable of being applied to variables of state (WF actual, IP),

References Cited

U.S. PATENT DOCUMENTS

4,593,523	A	6/1986	Hawes	60/34,281
5,303,541	A	4/1994	Goff et al.	60/773
6,148,601	A	11/2000	Jones et al.	60/773
2005/0284235	A1 *	12/2005	Kielb et al.	73/861,42

18 Claims, 4 Drawing Sheets



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$$A8- Z = \left[\frac{WF_{\text{measured}}}{IP} \right]$$

$$A9- Y = \left[\frac{WF_{\text{flow_meter}}}{X_{\text{metering_device}}} \right]$$

$$A10- U = [WF \text{ set-point or } X \text{ set-point}]$$

$$A11- Z_{n+1} = F \cdot Z_n + U_n$$

$$Y_{n+1} = H \cdot Z_n$$

A12 NOTATIONS

Xconsigne: metering device position sought
 WFconsigne: mass fuel flow sought
 WFreal: mass flow actually delivered by the metering system
 WFdebitmetre mass flow measured by the flow meter
 ~WFdebitmetre estimated mass flow
 ΔWFreal correction of actual mass flow
 Xdoseur measured position of the metering device slide valve
 ~Xdoseur estimated position of the metering device slide valve
 Rdebitmetre residue of mass flow
 Rdoseur residue of the position of the metering device slide valve
 IP vector of parametric unknowns
 ΔIP correction vector of vector of parametric unknowns
 K correction gain matrix
 z vector of state of filter
 Y vector of estimated outputs
 U vector of set-point inputs
 H output matrix
 F state matrix
 Q matrix of covariance of the state interference
 v state interference
 R matrix of covariance of measurement interference
 w measurement interference

What is claimed is:

1. A device for determining a measurement of mass fluid flow for a combustion chamber comprising a fluid metering device and a means of measuring the position of metering device known as the measured position, said device comprising:

a mass flow meter for measuring a mass flow of fluid known as the measured flow,

a hybridisation device suitable for determining an actual mass flow of fluid comprising:

a first input comprising a set-point value (WFset-point) of the mass flow sought or a set-point value (Xset-point) of the position of the metering device sought,

a prediction unit capable of determining, from the first input and variables of state comprising the actual mass flow (WFactual) and parametric unknowns (IP), estimated values comprising the estimated position of the metering device (Xmetering device) and the estimated mass flow (AWF flow meter),

a second input comprising the measured position of the metering device (Xmetering device) and the measured fluid mass flow (WFflow meter),

a calculator of residues capable of determining a first residue (Rmetering device) between the measured position of the metering device and the estimated

position of the metering device and a second residue (Rflow meter) between the measured fluid mass flow and the estimated fluid mass flow,

a correction unit capable of determining from the first and second residues corrections capable of being applied by the prediction unit to the variables of state (Wfactual, IP).

2. A device according to claim 1, wherein the prediction unit comprises a dynamic model at the state linking the first input to the variables of state and estimated values.

3. A device according to claim 1, wherein the correction unit comprises a correction gain matrix whose coefficients are fixed.

4. A device according to claim 1, wherein the correction unit comprises a correction gain matrix whose coefficients are variable.

5. A device according to claim 1, wherein the correction unit comprises a correction gain matrix whose coefficients are variable and the coefficients are determined by a mathematical law dependent on the mass flow of fluid or on the position of the metering device.

6. A device according to claim 1, wherein the correction unit comprises a correction gain matrix whose coefficients are variable and the correction gain matrix is a gain matrix of the Kalman filter (K), determined dynamically.

7. A device according to claim 1, wherein the correction unit comprises a correction gain matrix whose coefficients are variable the correction gain matrix is a gain matrix of the Kalman filter (K), determined dynamically by the use of matrices relating to the interference, submitted to continuous adaptation of their coefficients.

8. A device according to claim 1, wherein the first input further comprises a measured value of the temperature of the fluid (Tfuel).

9. A device according to claim 1, wherein the second input comprises a measured value of a pressure differential through the fluid metering device (δPmeasurement), the estimated values comprise an estimated value of this pressure differential (δPmeasurement), the residue calculator is capable of determining a third residue (RδP), between the measured value and the estimated value of the pressure differential, and the correction unit is capable of determining, from the first, second and third residues, corrections suitable for application by the prediction unit to the variables of state.

10. A process of determining a measurement of mass flow of a fluid for a combustion chamber, said process comprising the steps of:

a- entering a set-point value (WFset-point) of the mass flow sought or a set-point value (X set-point) of the position of the metering device sought, and variables of state comprising the actual mass flow (WF actual) and parametric unknowns (IP),

b- determining from step a- estimated values comprising the estimated position of the fluid metering device (X metering device) and the estimated mass flow (~WF-flow meter),

c- measuring the mass flow of fluid (WFflow meter) from a mass flow meter and the position of the fluid metering device (Xflow meter),

d- calculating a first residue (Rmetering device) between the measured position of the metering device and the estimated position of the metering device and a second residue (Rflow meter) between the measured mass flow of fluid and the estimated mass flow of fluid,



US007186550B2

(12) **United States Patent**
Choo et al.(10) **Patent No.:** **US 7,186,550 B2**
(45) **Date of Patent:** ***Mar. 6, 2007**(54) **NUCLEIC ACID MOLECULE**(75) Inventors: **Kong-Hong Andy Choo**, Doncaster East (AU); **Desiree Du Sart**, Doncaster (AU); **Michael Robert Cancilla**, Maribyrnong (AU)(73) Assignee: **Murdoch Childrens Research Institute**, Parkville (AU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 296 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/728,552**(22) Filed: **Dec. 2, 2000**(65) **Prior Publication Data**

US 2003/0096398 A1 May 22, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/078,294, filed on May 13, 1998, now Pat. No. 6,265,211.

(30) **Foreign Application Priority Data**May 13, 1997 (AU) PO6784
Aug. 26, 1997 (AU) PO8791(51) **Int. Cl.**
C12N 15/63 (2006.01)
C07H 21/04 (2006.01)(52) **U.S. Cl.** **435/320.1; 536/23.1**(58) **Field of Classification Search** **435/320.1; 536/23.1, 24.1; 514/44**

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**

5,712,134 A 1/1998 Hadlaczky

5,721,118 A 2/1998 Scheffler
6,265,211 B1 * 7/2001 Choo et al. 435/320.1**FOREIGN PATENT DOCUMENTS**WO WO 96/40965 12/1996
WO WO 98/08964 3/1998**OTHER PUBLICATIONS**Abeliovich, D. et al., "dup(10q) Lacking α -satellite DNA in Bone Marrow Cells of a Patient With Acute Myeloid Leukemia", *Cancer Genet. Cytogenet.*, 89:1-6 (1996).Choo, K. H. Andy, "Chromatin Dynamics '97. Centromere DNA Dynamics: Latent Centromeres and Neocentromere Formation", *Am. J. Hum. Genet.*, 61:1225-1233 (1997).Depunet, Theresa W., "Characterization of neo-centromeres in marker chromosomes lacking detectable alpha-satellite DNA", *Human Molecular Genetics*, 6(8):1195-1204 (1997).Du Sart, D. et al., (1997) "A functional neo-centromere formed through activation of a latent human centromere and consisting of non-alpha-satellite DNA", *Nature Genetics*, 16:144-153.Harrington J.J., et al., (1997) "Formation of de novo centromeres and construction of first-generation human artificial microchromosomes", *Nature Genetics*, 15:345-355.Ikono, M., et al., (1998) "Construction of YAC-based mammalian artificial chromosomes", *Nature Biotechnology* 16:431-439.Voullaire, L.E., et al., (1993) "A Functional Marker Centromere with No Detectable Alpha-Satellite, Satellite III, or CENP-B Protein: Activation of a Latent Centromere?", *Am. J. Hum. Genet.* 52:1153-1163.

* cited by examiner

Primary Examiner—Celine Qian(74) *Attorney, Agent, or Firm*—Scully, Scott, Murphy & Presser, P.C.(57) **ABSTRACT**

The present invention is directed generally to an isolated nucleic acid molecule encompassing a neocentromere or a functional derivative thereof or a latent, synthetic or hybrid form thereof and its use inter alia in developing a range of eukaryotic artificial chromosomes including mammalian (e.g. human) and non-mammalian an artificial chromosomes. Such artificial chromosomes are useful in a range of genetic therapies.

20 Claims, 223 Drawing Sheets

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taaaaaagtt gacgtgtaaa atccatgttaa aaaaagttggc agaagaagaca aactgtgtaaa	300
gcagcagcttc ttcattttctc atttcattcaa acagagatta ttaacagcct agcaagaacaa	360
cagtatccag gaaaaatcaa agattatcaa gctcatgttc tataatcaag caattttataa	420
actagacagaa gaacaagaca gatgataaag aacttgggta tattttaaatg ctagaagatt	480
caattcaaat aaatgtcc	498

The invention claimed is:

1. An isolated nucleic acid molecule comprising a neocentromere, wherein said neocentromere comprises a region of an eukaryotic chromosome and does not have any detectable alpha satellite DNA as determined by fluorescent in situ hybridisation (FISH), wherein said nucleic acid molecule comprises SEQ ID NO: 3, and wherein said nucleic acid molecule, when introduced into a cell, is capable of replicating, acting as an extra-chromosomal element and segregating with cell division.

2. The isolated nucleic acid molecule according to claim 1 wherein the eukaryotic chromosome is a mammalian chromosome.

3. The isolated nucleic acid molecule according to claim 2 wherein the chromosome is a human chromosome.

4. The isolated nucleic acid molecule according to claim 2 wherein the nucleic acid molecule binds to centromeric binding proteins (CENP)-A and -C or antibodies thereto.

5. The isolated nucleic acid molecule according to claim 3 wherein the chromosome is human chromosome 10.

6. The isolated nucleic acid molecule according to claim 5 wherein said neocentromere comprises a region mapping between q24 and q26 on said human chromosome 10.

7. The isolated nucleic acid molecule according to claim 3 wherein said human chromosome is a mardel (10) chromosome.

8. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is in linear form and co-introduced into a cell together with a telomeric sequence.

9. The isolated nucleic acid molecule according to claim 8 wherein the eukaryotic chromosome is a mammalian chromosome.

10. The isolated nucleic acid molecule according to claim 9 wherein said nucleic acid molecule binds to CENP-A and CENP-C antibodies.

11. The isolated nucleic acid molecule according to claim 9 wherein the mammalian chromosome is human chromosome 10.

12. The isolated nucleic acid molecule according to claim 11 wherein the neocentromere comprises a region mapping between q24 and q26 on said human chromosome 10.

13. The isolated nucleic acid molecule according to claim 8 wherein said chromosome is a human mardel (10) chromosome.

14. A genetic construct comprising an origin of replication for a eukaryotic cell and the nucleic acid molecule of claim 1, operably linked to telomeric nucleotide sequences functional in the cell in which the genetic construct is to replicate and wherein said genetic constructs when introduced into a cell, is a replicating, extra-chromosomal element which segregates with cell division.

15. The genetic construct according to claim 14 wherein the eukaryotic chromosome is a mammalian chromosome.

16. The genetic construct according to claim 15 wherein the eukaryotic chromosome is a human chromosome.

17. The genetic construct according to claim 16 wherein the nucleic acid molecule binds to CENP-A and -C or antibodies thereto.

18. The genetic construct according to claim 17 wherein the neocentromere is from human chromosome 10.

19. The genetic construct according to claim 18 wherein the neocentromere comprises a region between q24 and q26 on said human chromosome 10.

20. The genetic construct according to claim 18 wherein said chromosome is a human mardel (10) chromosome.

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